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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/997,683	11/15/2001	Avi J. Ashkenazi	P2730P1C32	4971

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EXAMINER	
WEGERT, SANDRA L	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 03/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/997,683	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	Sandra Wegert	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 February 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *119-124* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *119-124* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 November 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/31/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Action

Status of Application, Amendments, and/or Claims

The Preliminary Amendment, submitted 4 September 2002, and the Information Disclosure Statement, submitted 31 May 2002, have been entered. Claims 1-118 have been cancelled. Claims 119-124 have been entered.

Claims 119-124 are under examination in the Instant Application.

Informalities

Specification

The disclosure is objected to because of the following informalities:

URL's

The disclosure is objected to because it contains browser-executable code. This occurs, for example, in paragraph 2921. All URL's should be removed from the Specification. Applicant may refer to web sites by non-executable name only. See MPEP § 608.01 (p).

Appropriate correction is required.

Continuity

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows: The Provisional patent applications listed in the first paragraph of the instant specification do not refer to SEQ ID NO: 351, SEQ ID NO: 350, PRO 1153, or Figure 246. Therefore, for this Office Action, the filing date of 15 November 2001 of the instant Application is considered as the priority date.

Claim Rejections/Objections

Claim Rejections - 35 USC § 101 and 35 USC § 112, first paragraph

The following is a quotation of 35 U.S.C. 101:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 119-124 are rejected under 35 U.S.C. 101 because the claimed invention lacks a credible, specific and substantial asserted utility or a well-established utility.

The claims are directed to antibodies made against the polypeptide of SEQ ID NO: 351 (see Specification: Figure 246, *PRO1153* or *DNA59842-1502*). Further limiting claims are presented to monoclonal antibodies, humanized antibodies, antibody fragments, labeled antibodies, and antibodies that bind "specifically" to the polypeptide. However, the specification does not disclose a function for the antibodies against SEQ ID NO: 351, in the context of the cell or organism.

No well-established utility exists for newly isolated complex biological molecules. However, the specification implies that the following are credible, specific and substantial patentable utilities for the claimed antibodies:

1) In assays to screen for compounds capable of modifying the interaction between receptor and ligand.

2) To bind the polypeptide of SEQ ID NO: 351.

3) To treat cancer.

Each of these shall be addressed in turn.

1) in assays to screen for compounds capable of modifying the interaction between receptor and ligand. This asserted utility is also credible and substantial but not specific. Such can be performed for any receptor-ligand pair. Additionally, the specification discloses nothing specific or substantial for the compounds that can be identified by this method.

2) To bind the polypeptide of SEQ ID NO: 351. This asserted utility is credible and substantial, but not specific. Antibodies can be made to *any polypeptide.* However, if the specification discloses nothing specific and substantial about the polypeptide, both the polypeptide and its antibodies have no patentable utility.

3) To treat cancer. Table 9B of the instant Specification sets forth the results of assays to determine the number of clone copies in a variety of tissues. A ΔCt of >1 was typically used as the threshold value for amplification scoring, as this represents a doubling of gene copy. The ΔCt values indicate that significant amplification of nucleic acid DNA59842-1502 encoding PRO1153 occurred in several epithelial tumors; The Specification implies that antagonists (e.g.,

antibodies) directed against the protein encoded by DNA59842-1502 (PRO1153) would be expected to have utility in cancer therapy.

However, a slight increase in clone copies in several tumor types is not indicative of a specific or substantial utility for PRO1153 for use as an agent to treat cancer. A slight increase in clone numbers in a cancerous tissue is no doubt due to an increased number of chromosomes, a very common characteristic of cancerous and non-cancerous epithelial cells (see, for example: Hittelman, W., 2001, Ann. NY. Acad. Sci., 952: 1-12, especially pages 8 and 9, and; Crowell, et al, 1996, Cancer Epidemiol. 5: 631-637), not because PRO1153 plays a significant role in tumor formation or growth. The asserted utility is therefore not specific. Experiments confirming the specificity and substantial utility of PRO1153 in terms of mRNA and protein expression were not performed. Antibodies against PRO1153 were not administered to animals to test their anti-cancer effects. Significant further experimentation would be required of the skilled artisan to determine whether PRO1153 is expressed in certain cancers to the extent that antagonists (e.g., antibodies) directed against the protein encoded by DNA59842-1502 (PRO1153) would be expected to have utility in cancer therapy. Thus, the asserted utility is not substantial. In addition, the Specification shows that gene copy number is increased in certain tumor tissue samples. However, it does not necessarily follow that an increase in gene copy number results in increased gene expression and increased protein expression, such that the antibodies would be useful diagnostically or as a target for cancer drug development. For Example, Pennica et al (1998, PNAS 95: 14717-14722) disclose that:

"An analysis of WISP-1 gene amplification and expression in human colon tumors showed a correlation between DNA amplification and overexpression, whereas overexpression

of WISP-3 RNA was seen in the absence of DNA amplification. In contrast, WISP-2 DNA was amplified in the colon tumors, but its mRNA expression was significantly reduced in the majority of tumors compared with the expression in normal colonic mucosa from the same patient," (page 14722, second paragraph).

Furthermore, although the specification teaches that PRO1153 is expressed in several epithelial cancers (Table 9B), the state of the art is such that protein expression levels cannot be accurately predicted from the level of corresponding mRNA transcript, and therefore cannot be correlated to antibody binding. Haynes et al, for example, studied 80 proteins relatively homogeneous in half-life and expression level, and found no strong correlation between protein and transcript levels (Haynes et al., 1998, Electrophoresis 19:1862-1872). That research group found that for some genes, equivalent mRNA levels translated into protein abundances which varied by more than 50-fold (pg 1863, paragraph 2, Figure 1). Therefore, one skilled in the art cannot predict that the PRO1153 mRNA transcript levels determined in various cancerous tissues are indicative of PRO1153 polypeptide expression in cancerous cells. Undue experimentation is required by the skilled artisan to detect and quantify PRO1153 polypeptide expression in all possible tumor tissues/cells, other than lung or epithelial cancer.

Claims 119-124 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention. Thus, because the polypeptide of SEQ ID NO: 351 has not been shown to be useful, antibodies made against the polypeptide also have no specific use.

Applicants have implied that the PRO1153 polypeptide is a secreted protein, which posseses amino acid sequence identity with protein *HPBRII-7* (Fleischhauer, K., 1995, Accession No. CAA47751). However, the polypeptide of SEQ ID NO: 351 bears low (20-28%) sequence identity to *HPBRII-7*, which itself does not have a specific function.

Generally, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. For example, Skolnick et al. (2000, Trends in Biotech. 18:34-39) state that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function (see Box 2, p. 36). Similarly, Bork (2000, Genome Research 10:398-400) states that the error rate of functional annotations in the sequence database is considerable, making it even more difficult to infer correct function from a structural comparison of a new sequence with a sequence database (see especially p. 399). Such concerns are also echoed by Doerks et al. (1998, Trends in Genetics 14:248-250) who state that (1) functional information is only partially annotated in the database, ignoring multi functionality, resulting in underpredictions of functionality of a new protein and (2) overpredictions of functionality occur because structural similarity often does not necessarily coincide with functional similarity. Examples from the secreted polypeptide art demonstrate, in some cases, polypeptides with high homology having a wide-variety of functions in organisms (see Hesselgesser, et al, 1997, Methods in Enzymology, 287: 59-69, see pages 59 and 64-66) and in other cases, many different possible structures for secreted proteins that are considered related as to function (Blease, et al, 2000, Resp. Res., 1(1): 54-61). However, Applicants have not associated the disclosed PRO1153 polypeptide with any type or genus of polypeptide.

Therefore, based on the discussions above concerning the specific examples of structurally similar proteins that have different functions, along with the art's recognition that one cannot rely upon structural similarity alone to determine functionality, the specification fails to teach the skilled artisan how to use the claimed antibodies against PRO1153 without resorting to undue experimentation to determine what the specific biological activities of the PRO1153 polypeptide are.

The specification does not teach the skilled artisan how to use the claimed antibodies directed to the polypeptide of SEQ ID NO: 351 for any purpose. For example, there is no disclosure of particular disease states correlating to an alteration in levels or forms of the polypeptide such that the claimed antibody could be used as a diagnostic tool. The skilled artisan is not provided with sufficient guidance to use the claimed antibodies for any purpose.

Due to the large quantity of experimentation necessary to determine an activity or property of the disclosed polypeptide such that it can be determined how to use the claimed antibodies directed against SEQ ID NO: 351 and to screen for activity, the lack of direction/guidance presented in the specification regarding same, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art establishing that biological activity cannot be predicted based on structural similarity to other similar polypeptides, the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite particular biological activities- undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

35 USC § 112, first paragraph – Deposit Rules

Claims 119-124 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The invention appears to employ novel nucleic acid molecules (i.e., clone: DNA59842-1502). Since the nucleic acid molecules are essential to the claimed invention they must be obtainable by a repeatable method set forth in the specification or otherwise readily available to the public. If the nucleic acid molecules are not so obtainable or available, the requirements of 35 U.S.C. § 112 may be satisfied by a deposit of the nucleic acid molecules. The Specification at paragraphs 4442-4444 states that the deposit was made under the Budapest treaty. However, Applicants have failed to provide a copy of the deposit receipt. If a deposit is made under the Budapest Treaty, then an affidavit or declaration by Applicant, or a statement by an attorney of record over his or her signature and registration number, stating that the specific nucleic acid molecules have been deposited under the Budapest Treaty and that the nucleic acid molecules will be irrevocably and without restriction or condition released to the public upon the issuance of a patent, would satisfy the deposit requirement made herein. If a deposit is not been made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 C.F.R. §§ 1.801-1.809, Applicant may provide assurance of compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that

(a) during the pendency of this application, access to the invention will be afforded to the Commissioner upon request;

(b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;

(c) the deposit will be maintained in a public depository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer;

(d) a test of the viability of the biological material at the time of deposit will be made (see 37 C.F.R. § 1.807); and

(e) the deposit will be replaced if it should ever become inviable. Applicant's attention is directed to M.P.E.P. §2400 in general, and specifically to §2411.05, as well as to 37 C.F.R. § 1.809(d), wherein it is set forth that "the specification shall contain the accession number for the deposit, the date of the deposit, the name and address of the depository, and a description of the deposited material sufficient to specifically identify it and to permit examination." Finally, Applicant is advised that the address for the ATCC has recently changed, and that the new address should appear in the specification.

The new address is:

American Type Culture Collection
10801 University Boulevard
Manassas, VA 20110-2209

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 119 and 124 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 119 recites an antibody that binds a protein. Claim 124 recites an antibody that "specifically binds to" the same protein. Neither the Specification nor the art provide unambiguous definitions for "binds" and "specifically binds;" therefore, the metes and bounds of the claims cannot be determined by one skilled in the art. Furthermore, since antibodies are generally seen as binding antigens with both high affinity *and* high specificity, it is not known what additional characteristics would be displayed by an antibody binding "specifically."

Conclusion: Claims 119-124 are rejected for the reasons recited above.

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sandra Wegert whose telephone number is (571) 272-0895. The examiner can normally be reached Monday - Friday from 9:00 AM to 5:00 PM (Eastern Time). If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Kunz, can be reached at (571) 272-0887.

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SLW
3/10/04

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER